



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,540	05/02/2002	Audrey Goddard	P3230R1C001-168	1054

30313 7590 03/30/2005

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/063,540

Applicant(s)

GODDARD ET AL.

Examiner

Jegatheesan Seharaseyon

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 May 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9/29/2004.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment and Declarations under 37 CFR § 1.132, both submitted 29 September 2004, have been entered. Claim 1 is amended. Claim 6 is cancelled. Claims 1-5 is under examination in the Instant Application.
2. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.
3. The Office acknowledges the receipt of the drawings on 5/2/2002.
4. The Office acknowledges the change in title.
5. The Office also acknowledges the removal of embedded hyperlinks.
6. The Applicants have provided a copy of the sequence listing in response to the "Notice to Comply".
7. Applicants request for correction of inventorship under 37 CFR 1.48(b) is acknowledged.
8. The Office acknowledges the submission of the IDS dated 9/29/2004.
9. All pending rejections of claim 6 are withdrawn because Applicants have cancelled claim 6.

Priority

10. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of the filing date of August 24, 2000 based on the disclosure in the PCT Application PCT/US00/23328 filed 8/24/2000 of the differential tissue expression distribution in tumor versus normal tissue (example 18). Although, the previous patent

application discloses the same polypeptide (SEQ ID NO: 34) sequence as the instant specification, the disclosure is not enabling for the instant invention and therefore do not impart utility to the claims of the current application. Therefore, the filing date of 2 May 2002 is maintained as the priority date.

35 USC § 112, second paragraph, withdrawn

11. The rejection of claims 1-6 under 35 USC 112, second paragraph for being vague and indefinite, as set forth in the Office Action of 28 June 2004 is withdrawn in response to Applicants amendments and arguments.

35 U.S.C. § 101/112, first paragraph, Lack of Utility, Enablement, maintained

12. Claims 1-5 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under 35 U.S.C. § 101 are set forth at pp. 3-8 of the previous Office Action (28 June 2004). Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (28 June 2004), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (29 September 2004, page 6) that the results presented in the instant specification are enabling for the polypeptide of SEQ ID NO: 34 and antibodies directed against polypeptide. They argue that the utilities of PRO1277 polypeptide include the use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1277 cDNA is more highly expressed normal esophagus

Art Unit: 1647

tissue or normal skin compared to esophagus tumor tissue or melanoma tissue.

Applicants have also extensively discussed the utility guidelines (pages 6-8).

Applicant's arguments (29 September 2004) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing that polynucleotide is more highly expressed in normal esophagus or skin compared to esophagus tumor or melanoma tissue. However, there is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the normal tissue compared to the tumor tissue and as such one of skill in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility. In fact there is no disclosure to indicate if the PRO1277 polypeptide is expressed in normal or tumor stomach and skin tissues. Furthermore, as discussed extensively by Pennica et al. in the previous Office Action (28 June 2004, page 7), what is often seen is a *lack* of correlation between DNA amplification and increased gene expression.

As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer

Art Unit: 1647

samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (abstract). In addition, it is stated that no significant correlation between mRNA and protein expression was found ($r=-0.025$) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance.

Given the increase in amplified DNA (DNA copy number) for PRO1277 in the in normal esophagus or skin compared to esophagus tumor or melanoma tissue, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a ~~more~~ higher expression of mRNA would correlate with increased polypeptide levels. Further research needs to be done to determine whether the

Art Unit: 1647

decrease of PRO1277 cDNA expression compared normal esophagus or skin tissues supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial.

This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in *Brenner v.*

Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,

"a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed antibodies directed to PRO1277 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The declarations of Mr. Grimaldi, filed under 37 CFR 1.132 (29 September 2004), is insufficient to overcome the rejection of claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Similarly, the declaration of Dr. Polakis, filed under 37 CFR 1.132 (29 September 2004), is insufficient to overcome the rejection of claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Likewise, the declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (29 September 2004), is insufficient to overcome

the rejection of claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

In the declaration filed under 37 CFR 1.132 (29 September 2004, originally filed in application serial number 10/063,557), senior research associate Mr. Grimaldi states (page 2, paragraph 5), that "data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual". In addition, Mr. Grimaldi's declaration on paragraphs 6 and 7 states that semi-quantitative analysis employed to generate the data of example 18 is sufficient to determine if a gene is over or under expressed in tumor cells compared to corresponding normal tissue. Further it asserted that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor. It is further stated that additional studies can then be conducted if further information is desired. In paragraph 7, declarant indicates that the difference in the expression is expected to be reflected in the difference in the corresponding protein. However, this appears to be declarant's opinion, and is not supported by fact or evidence. There is no description in the specification that would indicate a correlation with higher or lower expression levels of the message to the PRO1277 polypeptide. It remains that, there is no information on the record as to whether the claimed protein is expressed at all in the esophagus and skin tissue, cancerous or otherwise.

Art Unit: 1647

Furthermore, it remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Applicants citing the second Grimaldi declaration (exhibit 2) filed under 37 CFR § 1.132 argues that, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed..... this same principal applies to gene under-expression." Again citing paragraph 5, Applicants contend that 'the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for the diagnosis and treatment."

At paragraph 4 of the second Grimaldi declaration (Exhibit 2), the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO 1136 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PR01136 gene is known to occur. All that the specification demonstrates is that the PRO1277 nucleic acid was more highly

Art Unit: 1647

expressed in normal esophagus and skin tissue compared to esophagus and melanoma tumor tissues. No mutation or translocation of PRO1277 has been associated with esophagus or skin cancer. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PR01136 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed polypeptides.

The Polakis Declaration states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to down regulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

Applicants also refer to three additional articles (Orntoft et al., Hyman et al., and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicants characterize Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed

Art Unit: 1647

corresponding increase in mRNA transcripts. Applicants further characterize Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. It is also claimed by the Applicants that Pollack et al. teach that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels.

Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual gene, which may or may not be in a chromosomal region, which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO1277 in the instant specification. That is, it is not clear whether or not PRO1277 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear. Hyman et al. also used CGH approach in their research. Less than half (44%) of highly amplified genes showed over expression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the polypeptides of the instant invention. Pollack et al. using CGH technology, concentrate on large chromosome regions showing high amplification (p.12965). However, Pollack et al. did not investigate or

Art Unit: 1647

show a relationship with amplification and polypeptide expression. In fact the authors caution that elevated expression of an amplified gene cannot alone be considered strong independent evidence of candidate oncogene's role in tumorigenesis. Thus, these references collectively do not teach as Applicants contend that there is a direct correlation between increased mRNA levels and increased levels of encoded protein. Accordingly, the Applicants' assertions that the PRO1277 polypeptides have utility in the cancer diagnostics are not substantial.

Applicants also contend that the claimed antibodies would have diagnostic utility even if there is no positive correlation between gene expression and expression of the encoded polypeptide. Further, it is asserted that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1277, the polypeptide encoded by a gene that is over-expressed or under expressed in cancer would still have credible, specific and substantial utility. Applicants assert that this position is supported by the declaration filed under 37 CFR 1.132 (29 September 2004) by staff scientist Ashkenazi. It claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (pages 1-2, Declaration, 29 September 2004) and to identify cancers for which there was an absence of gene product over-expression (page 2). The Ashkenazi declaration further argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment.

Applicants argue (Response, 29 September 2004, page 14) that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by Hanna et al. (attached to the Response of 29 September 2004).

Applicants contend that the publication teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically.

Applicants' arguments and declarations have been fully considered but are deemed not to be persuasive. In the instant application gene expression studies were conducted using pooled samples of normal and tumor tissues. With reference to Grimaldi reference, this appears to be declarant's own opinion, and is not supported by fact or evidence. In addition, one cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in copy number, or alternatively due to increase in transcription rates. It is important to note that the instant specification provides no information regarding differential mRNA levels of PRO1277 in normal esophagus or normal skin compared to esophagus tumor or melanoma tissue samples. The specification describes only gene amplification data.

The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. The declaration does not provide data such that the examiner can independently draw conclusions. In addition, there is no evidentiary art that would corroborate for example, that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue." Furthermore, as indicated above the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Haynes et al. and Hu et al discussions above). It is also not known whether PRO1277 polypeptide is expressed in normal esophagus and skin tissue and what the relative levels of expression are in these tissues. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1277 is amplified at higher levels in normal esophagus or normal lung compared to esophagus tumor and melanoma tissues, and invite the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted if further information is desired" (Appendix 1, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 101 utility for the claimed protein.

Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding differential mRNA levels of PRO1277 in tumor samples as contrasted to normal tissue samples or the corresponding protein levels. Only gene

Art Unit: 1647

amplification data were presented. Therefore, the declaration is insufficient to overcome the rejection of claims 1-5 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). In addition, as discussed above Chen et al. disclose that the correlation between mRNA expression and protein expression is poor at best.

The declaration of Ashkenazi appears to argue that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1277, the polypeptide encoded by a gene that is over-expressed or under expression in cancer would still have credible, specific and substantial utility. The examiner agrees that evidence regarding lack of over-expression would be useful.

However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Although, Applicants agree that Sen reference teaches that most cancerous tissues are aneuploid, it is argued on page 10, 3rd paragraph of remarks that there is no relevance to the expression levels and to the state of aneuploidy of the tumor cells with respect to the asserted utility. Applicants claim regardless of the cause of the differential expression, the fact that there is a higher level or lower level of expression of PRO1277 gene in normal esophagus or skin tissue compared to tumor containing esophagus and melanoma tissue allows this gene expression to be used as a diagnostic tool. These arguments have been fully considered but are found to be partially persuasive because the Office accepts that aneuploidy has no relevance to the differential expression of the cDNA in the instant invention. In addition, the lack of information on the record whether the claimed protein (PRO1277) is expressed at all esophagus and skin tissue, cancerous or otherwise would make significant further research a necessity.

At page 10, Applicants assert that they have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. It is also asserted that the Office relying on Pennica et al reference is also stating that data pertaining to PRO1277 polynucleotides do not necessarily indicate anything significant regarding the claimed PRO1277 polypeptides. Applicants further assert that the office is confusing the

Art Unit: 1647

relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other.

These arguments have been fully considered but are not found to be persuasive.

Haynes et al., Hu et al. and Chen et al. teachings listed above and discussed contradict,

Applicants assertion that there exists a direct correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers

against drawing conclusions based on small changes in transcript expression levels

between normal and cancerous tissues. The Office relied on Pennica et al. to teach

that, "it does not necessarily follow that an increase in gene copy number results in

increased gene expression". Pennica et al. on p.14722, clearly discuss the variability in

DNA amplification and gene expression. Contrary to Applicants assertion that "it is

possible that the apparent amplification observed for *WISP-2* may be caused by another

gene in this amplicon" (see bottom of p.10) further reading of Pennica et al. indicates

that the reduced expression of *WISP-2* in colon tumors and cell lines suggests that it

may function as a tumor suppressor. The Office agrees with the Applicants in that

the Pennica et al. reference does not discuss the relationship of level of mRNA and

level of protein expression. However, this reference was cited by the Office to show the

lack of correlation of between DNA amplification and gene expression. Although,

Applicants indicate on p.10 that there is a well established correlation in the art that the

level of protein is positively correlated to the level of mRNA, as indicated above Haynes

et al., Hu et al., and Chen et al. polypeptide levels cannot be accurately predicted from

mRNA levels. Therefore, there is no evidence to support Applicants' assertion that there

Art Unit: 1647

is working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. In addition, even if there was a correlation between mRNA levels and protein levels, Applicants have not established a nexus between the cDNA of instant invention and PRO1277 protein. As stated above and in the Office Action of 28 June 2004, the specification does not provide sufficient evidence or guidance to the skilled artisan to diagnose or treat any disease. Therefore, there would be no specific utility for antibodies of PRO1277 protein.

Whether or not increased levels of PRO1277 mRNA correlate with increased levels of PRO1277 protein is not an issue. The declarations and cited references do not establish a substantial utility for the claimed PRO1277 polypeptide molecules or the antibodies binding to such. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease.

Therefore, all of these reasons, the rejection of claims 1-5 based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office Action is maintained.

Claim Rejections - 35 USC § 103, withdrawn

13. The rejection of claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Sulston et al., Accession No: Q9UDNO or AAF19243, 21 December 1999 in view of Jacobs et al. (U.S. Patent No: 5 965 397) is withdrawn because of Applicants persuasive arguments.

14. No claims are allowed.

Art Unit: 1647

15. THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

Application/Control Number: 10/063,540

Page 19

Art Unit: 1647

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 3/05


JANET ANDRES
PRIMARY EXAMINER